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GB 1234699	BE A 0701032
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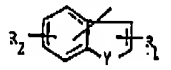
J Med Chem (1982) Vol 25 pages 145-152 J Med Chem (1978) Vol 21 pages 628-633

(58) Field of search
C2C

(54) Benzoic acid derivative

(57) Novel compounds of the formula A–CO–BD wherein A is a group of formula II or III



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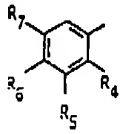


III

wherein the free valence is attached to either fused ring in formula II,

Y is $-CH_2-$, $-NR_3-$, $-O-$, or $-S-$,

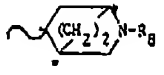
R_1 and R_2 are independently hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, amino, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, mercapto or (C_{1-4})alkylthio,

R_3 is hydrogen, (C_{1-6})alkyl; (C_{3-5})alkenyl, aryl or arylalkyl,

R_4 to R_7 are independently hydrogen, amino, nitro, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy, (C_{1-4})alkyl, (C_{1-4})alkanoylamino or pyrrolyl,

B is –O– or –NH–

D is a group of formula



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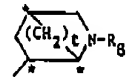

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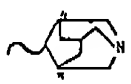
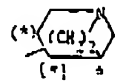


VIII,



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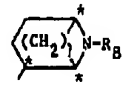

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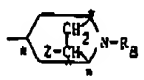

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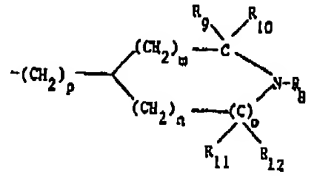

XII

wherein t is 1 or 2, l is 2 or 3, Z is C_{1-4}alkoxy, R_9 to R_{12} are independently H or C_{1-4} alkyl, m is 0, 1 or 2 n, o and p are independently 0 or 1 and R_8 is H, C_{1-7} alkyl, C_{3-5}alkenyl or aralkyl, (subject to certain provisos) are serotonin M antagonists.

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SPECIFICATION

Benzoic acid derivatives

This invention relates to benzoic acid derivatives.

It has been proposed (see for example J.R.Fozard in Advances in Neurology Vol. 33 Raven Press New York 1982) to use compounds with serotonin antagonistic effects, i.e. 5HT blocking effects, in the treatment of migraine. Particularly interesting are the compounds which antagonise the 5-HT M-receptors. A particular active compound of this type is Metoclopramide (US Patent 3177252) which J.B.Hughes in Med.J.Australia 2 No. 17, p.580 (1977) has reported to lead to an immediate beneficial effect on a migraine attack on slow I.v. injection of 10 mg.

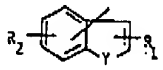
Subsequently further compounds with serotonin-M antagonistic effect has been described. European Publication 67770 describes a narrow class of tropane phenyl esters.

The present invention provides a new group of compounds which has not been specifically suggested before in the literature and which have particularly interesting pharmacological properties, for example, serotonin M antagonistic activity and antiarrhythmic agents, e.g. as indicated by potency in the vagus nerve test mentioned hereinafter.

The present invention provides in one aspect compounds of formula I

A–CO–B–D I

wherein A is a group of formula II or III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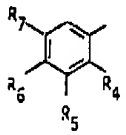

III

wherein the free valence is attached to either fused ring in formula II,

Y is $-CH_2-$, $-NR_3-$, $-O-$, or $-S-$,

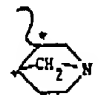
R_1 and R_2 are independently hydrogen, halogen, (C_{1-4}) alkyl, (C_{1-4})alkoxy, hydroxy, amino, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, mercapto or (C_{1-4})alkylthio,

R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-5})alkenyl, aryl or arylalkyl,

R_4 to R_7 are independently hydrogen, amino, nitro, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy, (C_{1-4})alkyl, (C_{1-4})alkanoylamino or pyrrolyl,

B is –O– or –NH–

D is a group of formula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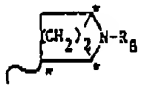
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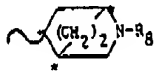
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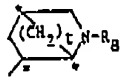
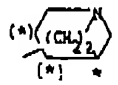

VII

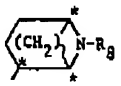
wherein t is 1 or 2,


VIII,



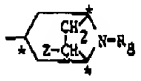
IX

wherein the bond is in the position 3 (*) or 4 [*],



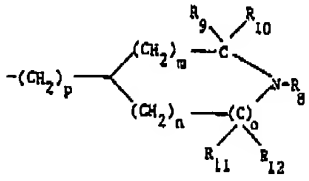
X

wherein 1 is 2 or 3,



XI

wherein Z is (C_{1-4})Alkoxy,



XII

wherein R_9 to R_{12} are independently hydrogen or (C_{1-4})alkyl,
m is 0, 1 or 2 and
n, o, p independently are 0 or 1,
wherein R_8 in each of formulae V to VII and X to XII is hydrogen, (C_{1-7})alkyl, (C_{3-6})alkenyl or aralkyl with the proviso that

1) when A is a group of formula III, and B is −NH−, then either D is a group of formula IV or R_5 is amino, (C_{1-4})alkylamino or di(alkyl(C_{1-4})amino and D is a group of formula XII other than 4-piperidinyl substituted by R_8 as defined above,

2) when A is a group of formula III, and B is −O− then D is other than a group of formula XII which is piperidinyl, pyrrolidinyl, pyrrolidinyl-2-methyl or azetidinyl, each substituted by R_8 as defined above,

3) when A is a group of formula II wherein Y is $-NR_3-$, −O− or −S−, R_2 is as defined above, and the free valence is in position 7 and B is −NH− then D is other than a group of formula V, X or XI,

4) When A is a group of formula II wherein Y is $-NR_3-$, R_3 is as defined above and wherein R_1 is in position 3 and is hydroxy or alkoxy, the free valence is in position 2 and B is −NH− then D is other than a group of formula XII which is pyrrolidinyl-2-methyl substituted by R_8 as defined above, and

5) when A is a group of formula II wherein Y is $-NR_3-$, R_2 is as defined above and wherein R_1 is in position 2 and is chlorine, bromine or substituted amino, the free valence is in position 3 and B is −O− then D is other than a group of formula XII which is a radical of formula $-(CH_2)_q-T$ wherein q is 0 or 1 and T is a 5 or 6 membered heterocyclic ring containing a nitrogen ring hereto atom, their acid addition salts and quaternary ammonium salts, hereinafter referred to as compounds of the invention.

A number of the compounds excluded from the above scope have been described as pharmaceuticals e.g. dopamine antagonists or anti-emetics, but none have been described as having serotonin-M antagonist activity.

Such compounds have been disclosed in respect of the provisos for example in the following representative publications:-

1) European Patent Publication 13138 and 94742, USP 2748138, DOS 2803651
2) J.Med.Chemistry, 1978, *21*, p.628 and 1982 *25*, p. 145 DOS 2434547
3) World Patent 84/03281
3) Belgian Patent 701023
5) DOS 2557342 and 2557341

None of these publications specifically disclose or suggest the present compounds.

Any alkyl molety preferably is methyl, ethyl or propyl. Alkoxy is preferably methoxy or ethoxy. Aralkyl is conveniently aryl(C_{1-4})alkyl. Alkenyl is preferably allyl or methally. Any aryl molety is preferably unsubstituted phenyl or phenyl mono- or poly-substituted by (C_{1-4})alkyl, e.g. methyl, halogen, e.g. fluorine, hydroxy, or (C_{1-4})alkoxy, e.g. methoxy. Preferably any substituted aryl group is mono-substituted. Aralkyl is conveniently benzyl. Halogen is fluorine, chlorine, bromine or iodine.

A is conveniently a group of formula II. In the group of formula II, the group −CO− may be attached to the ring carbon atom in position 2,3,4,5,6 or 7 of the nucleus, but preferably in position 4 and 5. Most preferably the −CO− group is attached to the ring containing Y, especially in position 3. Preferably A is indole.

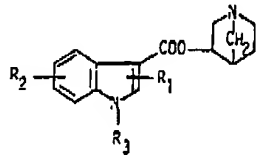
R_2 is attached to the ring carbon atom in position 4,5,6 or 7 of the nucleus, preferably position 5 and R_1 is

attached to the ring carbon atom in position 2 or 3 of the nucleus. Tautomers are also covered by formula I e.g. when R_1 is hydroxy or mercapto in the 2 position. R_5 is conveniently hydrogen or alkyl.

The groups of formula IV to XII may contain at least one asymmetric carbon atoms e.g. these marked * which may exist in different configurations and exist in different stereoisomeric forms. The compounds may exist in racemic or optically active form.

R_6 is preferably alkyl especially methyl.

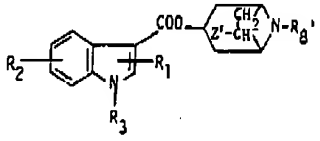
One preferred group of compounds comprises compounds of formula Ip



Ip

or salts thereof.

Another preferred group of compounds comprises compounds of formula Iq

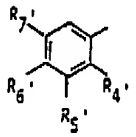


Iq

wherein R_8' is (C_{1-4})alkyl and

Z' is methoxy.

Preferred groups of formula III are of formula IIIa



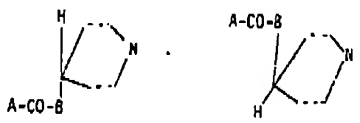
IIIa

wherein R_4' is (C_{1-4})alkoxy, especially methoxy, R_5' is hydrogen, R_6' is amino or (C_{1-4})alkylamino, especially methylamino and R_7' is halogen, especially chlor.

Of the compounds of formula I, the compounds having the group XII are prefarred especially ons of those wherein

a) m = 2, n = 0, o = 0, p = 1, R_9, R_{10} R_{11}, R_{12} = H and R_8 = CH_3,
b) m = 2, n = 0, o = 1, p = 0, R_9, R_{10}, R_{11}, R_{12} = H and R_8 = CH_3,
c) m = 1, n = 1, o = 1, p = 0, R_9, R_{10}, R_{11}, R_{12} = H and R_8 = CH_3,
d) m = 0, n = 1, o = 1, p = 0, R_9, R_{10}, R_{11}, R_{12} = H and R_8 = CH_3,
e) m = 1, n = 1, o = 1, p = 0, R_9, R_{10}, R_{11}, R_{12} = and R_8 = CH_3,
f) m = 2, n = 0, o = 0, p = 1, R_9, R_{10}, R_{11}, R_{12} = H and R_8 = CH_3,
g) m = 0, n = 1, o = 1, p = 1,
h) m = 1, n = 0, o = 1, p = 0,
i) m = 2, n = 1, o = 1, p = 0,
j) m = 1, n = 0, o = 1, p = 0,

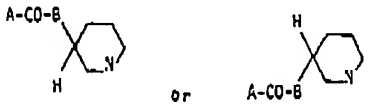
When D is a group of formula IV to XI, these can exist in two different configurations, i.e.



α or endo and β or exo

The two different configurations may be appreciated by making the groups having a configuration wherein a reference plane may be drawn through the carbon atoms of the ring and the nitrogen atom is above the plane and the alkylene bridge is below the plane. A group of formula IV to XI has the α configuration when the group A–CO–B– is below the plane on the same side as the alkylene bridge. This corresponds to the endo configuration and also to the configuration in tropine etc. A group of formula IV and XI has the β-configuration when it is above the plane on the same side as the nitrogen bridge. This corresponds to the exo configuration and also the configuration in pseudotropine etc. Used hereinafter is the exo/endo nomenclature. The endo isomers are preferred.

When D is a group of formula XII, this can exist in two different configurations: e.g.



R S

In particular the present invention provides a process for the production for a compound of formula I as well as acid addition salts thereof or quaternary ammonium salts thereof which includes the step of

a) condensing an appropriate compound of formula XIII

$$A-CO-OH \qquad XIII$$

wherein A is as defined above, a reactive derivative thereof, or a precursor of the acid or derivative, with an appropriate compound of formula XIV

$$H-B-D \qquad XIV$$

wherein B and D are as defined above, or a precursor of the compound or,

b) alkylating a compound of formula I having a secondary amino group to produce a compound of formula I with a tertiary amino group,

c) deprotecting any protected form of a compound of formula I to obtain a compound of formula I,

d) halogenating a compoud of formula I wherein A is a group of formula II and R_1 is hydrogen to obtain the corresponding compound wherein R_1 is halogen, or

e) alkoxylating a compound of formula I wherein A is a group of formula II and R_1 is halogen to obtain the corresponding compound wherein R_1 is alkoxy, and

recovering the resultant compound of formula I as such or as acid addition salt or as a quaternary ammonium salt thereof.

It is assumed that in all these reaction processes the configuration of the groups of formulae IV to XII remain unchanged.

The condensation process of the invention to obtain amides and esters may be effected in conventional manner for analogous compounds.

For example, the carboxylic acid group may be activated in the form of a reactive acid derivative, especially for the production of amides.

Suitable reactive acid derivatives may be formed as in situ as intermediates by reaction with N,N'-carbonyl-dimmidazole or with N-hdyroxy-succinimide. Alternatively an acid chloride may be used, e.g. produced by reaction with oxalyl chloride. In the case of sulphonic acids, the acid chloride is preferably used.

For production of esters, the alcohol may be used e.g. in the form of an alkali metal salt, preferably the lithium salt. Such salts may be produced in conventional manner, e.g. by reaction of a n-butyl lithium with the alcohol in tetrahydrofuran.

If desired a heterocyclic or tertiary amine, e.g. pyridine or trietylamine, may be present, especially for the production of amides.

Suitable reaction temperatures may be from about −10° to about 100°. Higher temperatures are preferably used for amides and for groups of formula IV and VIII.

Other suitable inert organic solvents include, e.g. tetrahydrofuran or dimethoxyethane.

The compounds of the invention may be converted into other compounds of the invention, e.g. in conventional manner. Some interconversions are exemplified in processes b),c),d) and e).

The alkylation reaction or process b) may be effected in conventional manner. Any free amino group may be alkylated, especially compounds of formula II wherein Y is NH.

Appropriate alkylation conditions include reaction with an alkyl halide in the presence of a sodium alcoholate. Suitable temperatures may be from −50° to about −30°C.

The deprotection reaction of process c) is specifically suitable for the production of compounds with secondary amino groups, e.g. R_8 = H or primary amino groups, e.g. $R_2 = NH_2$.

For example a compound of formula I may be produced in protected form, e.g. R_8 being replaced by a secondary amino protecting group such as benzyl.

The benzyl group may be split off in conventional manner, e.g. by hydrogenation to produce the corresponding compound of formula I wherein R_8 is hydrogen.

Suitably the hydrogenation may be effected in the presence of a palladium on active charcoal at room temperature or at a slightly elevated temperature. Suitable solvents include acetic acid, ethyl acetate or ethanol.

A primary amino group R_1 or R_2 may be protected by e.g. N-benzyloxycarbonyl. This group may be split off by hydrogenation analogously to that indicated above. In the presence of a benzyl group the N-benzyloxycarbonyl group is generally split off first so that this group may be selectively split off.

Also the amino group may be in the form of a nitro group. This can be selectively reduced in conventional manner, e.g. by iron in hydrochloric acid.

Halogenation according to process d) may be effected in conventional manner. For example with N-chloro-succinimide may lead to chlorination. Such reactions may be effected in a suspension in chloroform.

Replacement of reactive halogen groups according to process e) may be effected in conventional manner, e.g. by reaction with a appropriate alcohol at e.g. room temperature from 10 to 20 hours at least.

A precursor of a starting material may be employed if desired. Such a precursor may be capable of being converted into the starting material in conventional manner but instead the process of the invention is carried out with the precursor and the other starting material or materials or a precursor thereof. The resultant product is converted into the compound of the invention in conventional manner, e.g. by using the same reaction conditions by which the precursor may be converted into the starting material. Typical precursors include protected forms of a starting material, e.g. wherein amino groups are temporarily protected.

The compounds of the invention may be isolated and purified in conventional manner. If isometric mixtures of starting materials containing groups of formula XIV are used then the final compounds may be purified by e.g. column chromatography.

Free base forms of compounds of the invention may be converted into salt forms. For example acid addition salts may be produced in conventional manner by reacting with a suitable acid, and vice versa. Suitable acids for salt formation include hydrochloric acid, malonic acid, hydrobromic acid, maleic acid, malic acid, fumaric acid, methanesulphonic acid, oxalic acid, and tartaric acid. Quaternary ammonium salts of the compounds of the invention may be produced in conventional manner, e.g. by reaction with methyl iodide.

Insofar as the preparation of any particular starting material is not specifically described these are known or may be prepared in conventional manner.

In the following examples all temperatures are in degrees Centigrade and are uncorrected.

In the tables 1) = decomposition
FUM = base-demifumarate
2) Stereochemistry 1S*, 3r*, 5R*, 6R*
Hygfum = hydrogenfumarate

Example 1

1H-indo-3-yl-carboxylic acid-(3R,4S*)-1-azabicyclo-[2.2.1]hept-3-yl-ester* (exo form)

(Compound of formula I, wherein A = group of formula II, Y = $-NR_3-$, $R_1 = R_2 = R_3$ = H, Carboxyl group in position 3, B = −O−, D = group of formula IV; configuration : exo)

450 mg (4 mM) 1-azabicyclo[2.2.1]heptan-3-ol are treated dropwise with 4mM butyl lithium dissolved in hexane. The mixture is stirred for 1 hour at room temperature (25°C). The volume is concentrated to half.

The mixture is diluted with 10 ml dimethylformamide and treated with 1.69 g indol-3-yl carboxylic acid imidazolide (obtained in conventional manner by treating N,N'-carbonyl-imidazole with indol-3-yl carboxylic acid in dry tetrahydrofuren). The resultant solution is maintained at 50° for 12 hours and then partitioned between 1N aqueous sodium carbonate and methylene chloride. The organic phase is washed with water and concentrated to give 1.2 g of a white foam, which is chromatographed on a fifty-fold amount of silicagel using as eluant methylene chloride containing 5% methanol and 0.2% aqueous ammonia.

After 550 mg side products the title compound is eluted. The title compound is recrystallized from methylene chloride/hexane. M.p.t. 181-183° (decomposition).

In analogous manner the following compounds of formula I are produced:

Example	Formula II R_1	R_2	Y	Position of carbonyl group	B	Configuration	D= Group of formula	R_8	M.p.t.(°C)	Form
2	H	H	–NH–	3	–O–	endo	XI (Z = OCH_3)	CH_3	90-92	Hygfum
3	H	H	–NH–	3	–O–	(endo)	X (1 = 3)	CH_3	176-8	Base
4	H	H	–NH–	3	–O–	endo	V	CH_2	184-5	Base
5	H	H	–NH–	3	–O–	(endo)	X (1 = 2)	CH_3	189-90	Base
6	H	H	–NH–	3	–O–	(exo)	X (1 = 3)	CH_3	209-10[1)]	Base
7	H	H	–NH–	3	–O–	endo	IV	-	266-268	Hydrochloride
8	H	H	–NH–	3	–O–	exo	VII (t = 1)	CH_3	192-3[1)]	Base
9 (–)	H	H	–NH–	3	–O–	endo	V	CH_3	195-197	Base
10 (+)	H	H	–NH–	3	–O–	endo	V	CH_3	190-94	Base
11	H	H	–NH–	3	–O–	endo	VI	CH_3	140-48	FUM
12	H	H	–NH–	5	–O–	endo	XI (Z = OCH_3)	CH_3	155-58	Hydrochloride

( ) = Ring is in chair form

Example	Formula III R_4	R_5	R_6	R_7	B	Conf.	D = Group of formula	R_8	M.pt. (°C)	Form
13	OCH_3	H	$NHCH_3$	Cl	NH	exo	IV	–	254-55	Hydrochloride
14	OCH_3	H	$NHCH_3$	Cl	NH	endo	IV	–	237-38[1)]	Hydrochloride

Example 15

(-)-1H-Indolyl-3-carboxylic acid 2S-(1-methyl-2-pyrrolidinyl-methyl) ester

(Compound of formula I, A = group of formula II, Y = $-NR_3-$, $R_1 = R_2 = R_3 = H$, carbonyl group in position 3, B = –O–, D = group of formula XII, wherein o = n = O, m = 2, $R_6 = CH_3$, $R_9 = R_{10} = H$, p = 1, configuration: S)

a) *N-Methoxycarbonyl-L-proline*

57.5 g L-Proline are suspended in 300 ml pyridine and the resultant suspension added dropwise from 0° to 7° within 1 hour to a mixture of 39 ml chloroformic acid methyl ester and 30 ml of absolute methylene chloride. After finishing the addition an almost clear solution results which is allowed to stand over night at room temperature. The mixture is cooled to 0-5°. An approximately 10% hydrochloric acid solution is added until the mixture has a pH value of 1. The mixture is extracted 5 times with methylene chloride. The organic phases are combined, washed with water once, dried over sodium sulphate and concentrated twice by evaporation after the addition of toluene. The resultant heading compound is obtained in a form of a colourless solid which is dried at room temperature in a high vacuum.
$[\alpha]_D^{20} = -145°$ (c = 2.8 in water).

b *(-)-2-hydroxymethyl-N-methyl-pyrrolidine*

46 g lithium aluminium hydride are suspended in 500 ml tetrahydrofuran. A solution of 52 g N-methoxycarbonyl-L-proline in 500 ml tetrahydrofuran is added to the resultant suspension at 20 to 35°C. The mixture is heated to reflux temperature and refluxed for 24 hours. The mixture is then cooled to –10° and carefully treated dropwise with a mixture of 125 ml water and 125 ml tetrahydrofuran at –10 to 0°.

The mixture is allowed to react at room temperature and forms a white suspension. The white suspension is filtered off and the filter residue extracted three times with methylene chloride. The extracts are combined with the filtrate. The mixture is concentrated under a vacuum at 50° to give 32 g of an oil. This oil is distilled (17 mm Hg) under water vacuum.

1. Fraction 70°/17 mm = 500 mg[n]D $_{20}$ = 1.4665
2. Fraction 72°/17 mm = 4.4 g [n]D $_{20}$ = 1.4670
3. Fraction 75°/17 mm = 750 mg[n]D $_{20}$ = 1.4680
4. Fraction 80-85°/17 mm = 400 mg[n]D $_{20}$ = 1.4680

The 2nd Fraction contains the heading compound $[\alpha]_D^{20} = -51.9°$ (c = 1.65 in ethanol).

c *(-)-1H-indol-3-yl carboxylic acid -2S-(1-methyl-2-pyrrolidinylmethyl) ester*

3.45 g (-)-2-hydroxymethyl-N-methyl-pyrrolidine is dissolved in tetrahydrofuran and 18.7 ml butyl lithium in hexane is added at 10 to 18°. The resultant white suspension is stirred for 45 minutes at room temperature and concentrated in a water vacuum at 17 mm Hg to a volume of about 20 ml. After addition of 15 ml tetrahydrofuran the mixture is treated with 45 g indol-3-yl carboxylic acid chloride in 20 ml tetrahydrofuran at 10 to 16°. The resultant solution changes to a beige suspension which is allowed to stand for 4 hours. The mixture is partitioned between methylene chloride and an aqueous 1N sodium carbonate solution. The organic phase is evaporated to give a crystalline residue which is recrystallized once from ethyl acetate and once from methylene chloride/methanol to give the title compound.
M.pt. 162-163° (decomp), $[\alpha]^{20}_D = -30.0°$, (c = 0.85 ethanol).

In analogous manner (either via the acid chloride or the imidazolide) the following compounds of formula I are prepared.

	Formula II				*Formula XII*											
Example	R_1	R_2	*Y*	group position	*B*	*Conf.*	R_8	R_9	R_{10}	R_{11}	R_{12}	*m*	*n*	*o*	*p*	*M.pt.*	*Form*
16	H	H	–NH	–3	–O–R		CH_3	H	H	H	H	2	0	0	1	163-4[1)]	Base
17	H	H	–NH	–3	–O–RS		CH_3	H	H	H	H	1	0	1	0	185-6	Base
18	H	H	–NH	–3	–O–RS		CH_3	H	H	H	H	0	1	1	1	1409-2	Base
19	H	H	–NH	–3	–O–RS		CH_3	H	H	H	H	2	0	1	0	183-4	Base
20	H	H	–NH	–3	–O–RS		CH_3	H	H	H	H	1	1	1	0	216-7[1)]	Base
21	H	H	–NH	–3	–O–RS		H	CH_3	CH_3	CH_3	CH_3	1	1	1	0	281-3[1)]	FUM.
22	H	H	–NH	–3	–O–RS		CH_3	H	H	H	H	2	1	1	0	141-2	Base
23	H	H	–NH	–3	–NH–RS		H	H	H	H	H	1	0	1	0	230-1	Base
24	H	H	–NH	–3	–NH–RS		CH_3	H	H	H	H	1	0	1	0	208-7	Base

Example	Formula III R_4	R_5	R_6	R_7	B	Conf.	Formula XII R_8	R_9	R_{10}	R_{11}	R_{12}	m	n	o	p	M.pt.	Form
25	OCH_3	H	NH_2	Cl	NH	RS	H	H	H	H	H	1	0	1	0	165[1]	HOX
26	OCH_3	H	$NHCH_3$	Cl	NH	RS	CH_3	H	H	H	H	0	1	1	1	196-98	Hydro-chloride

The compounds of the invention exhibit pharmacological activity and are therefore useful as pharmaceuticals, e.g. for therapy.

In particular the compounds exhibit serotonin M receptor antagonist activity as indicated in standard tests. For example, in one test the action of the compounds in inhibiting the action of serotonin in reducing the amplitude of the compound action potential from the isolated rabbit vagus nerve was observed according to the principles of Ricciappo Neto, European Journal of Pharmacology (1978) *49* 351-356, under conditions permitting differentation between action potentials generated in myelinated nerve fibres (A fibres) and those generated in small non-myelinated fibres (C fibres) as described by B.Oakley and R.Schater, Experimental Neuorbiology, A Laboratory Manual, University of Michigan Press, 1978, p.85 to 96. Serotonin itself exerts its effect selectively on the C-fibres progressively with dosage. This action of serotonin is not blocked by the known serotonin antagonists, methtepine, methysergide, BOL - 148, which have been said to block D receptors for serotonin, but not M receptors (see Gaddam and Picarlli, Brit.J.Pharmacol. (1957), *12*, 323-328). It therefore appears that serotonin reduces the amplitude of the action potential carried by the C fibres through an effect mediated by M receptors for serotonin which are located on these nerve fibres.

The test may be effected by establishing a dose response curve for serotonin ($10^{-7} - 5 \times 10^{-6}$ M) after setting up the nerve. The serotonin is washed out and when the C fibre action potential has regained its original amplitude the compound of the invention at a set concentration of from about 10^{-10} M to about 10^{-6} M is preincubated with the nerve for 30 to 60 minutes. Varying concentrations of serotonin (10^{-7} to 10^{-4} M) are then applied with the compound of the invention at the concentration as was present during the preincubation period.

The M receptor antagonists of the invention either entirely block the action of serotonin (non-competitive antagonist) or cause a parallel shift of the serotonin/dose response curve to the right (i.e. increased concentrations of serotonin were required for effect) (competitive antagonist). The pD'_2 or pA_2 value may be obtained in the conventional manner.

The serotonin M receptor antagonist activity is also indicated by inhibiting the effect of serotonin on the isolated rabbit heart according to the method of J.R.Fozard and A.T.Moborak Ali, European Journal of Pharmacology, (1978), *49*, 109-112 at concentrations of 10^{-11} to 10^{-5} M of the compound of the invention. pD'_2 or pA_2 values may be calculated in the conventional manner.

The action of the compounds as serotonin M receptor atagonists for the treatment of analgesia is confirmed by action in the hot plate test at a dose of from about 0.1 to 100 mg/kg s.c. or p.o.

The serotonin M receptor antagonist activity is furthermore indicated in the cantharidine blister base test at a concentration of about 10^{-8} M. A blister is produced on the skin of the forearm of human volunteers with cantharidine. When serotonin is applied to the base of such blisters it produces pain which can be measured, the intensity being proportional to the concentration of serotonin applied. The procedure has been described by C.A.Keele and D.Armstrong in Substances producing Pain and Itch, Edward Arnold, London, 1964, p. 30 to 57. This algesic action of serotonin is not inhibited by the serotonin D receptorantagonists such as lysergic acid diethylamide or its bromo derivative and is therefore believed to be mediated by M receptors.

In the procedure followed the area under the curve instead of the peak amplitude is measured by a linear integrater coupled to a pain intensity indicator which is operated by the volunteer. With increasing concentrations of serotonin a cumulative dose-response curve to serotonin may be obtained. When no further response on increasing the serotonin concentration is obtained, the serotonin is washed off and the blister incubated with physiological buffer solution for at least 40 minutes before the compound of the invention is applied. The test substance is preincubated with the blister base for 30 minutes at a concentration of about 10^{-8} M before varying concentrations of serotonin are applied. A pA_2 value may be obtained in the conventional manner.

The compounds of the invention are therefore indicated for use as serotonin M receptor and antagonists, e.g. for the treatment of pain, especially migraine, vascular and cluster headaches and trigeminal neuralgia and also for the headaches of heart circulation disorders, e.g. for the treatment of sudden death, and possibly as anti-psychotics.

The compounds of the invention furthermore exhibit antiarrhythmic acitivity as indicated by their serotonin M receptor antagonist activity and in standard tests. For example the compounds inhibit arrhythmias induced by norepinerphrine in anaesthetized rats. In this test infusions of norepinerphrine (3 to 10 microgram/animal body weight) are given until an arrhythmic phase as indicated by ECG meseurements lasts longer than 10 seconds duration. After control of 3 consecutive injections of norephinephrine the compound of the invention is injected at from about 10 to about 500 microgram/kg animal body weight followed by norephinephrine injections. The arrhythmic phase is reduced, or abolished depending on the dose of test compound.

The compounds are therefore indicated for use as antiarrhythmic agents.

An indicated daily dose for the above indications is from about 0.5 to about 500 mg conveniently administered in dvidied doses 2 to 4 times a day containing from about 0.1 to about 250 mg.

The present invention accordingly provides a compound of the invention in pharmaceutically acceptable form, e.g. in free base form, or pharmaceutically acceptable acid addition salt form or quaternary ammonium salt form, for use as a pharmaceutical, particularly for use as a serotonin M antagonist for those diseases where blockage of serotonin M receptors would be expected to have beneficial effects, e.g. as an analgesic agent, especially as an anti-migraine and as an anti-arrhythmic agent.

The compounds of the invention may be administered in free base form, or in pharmaceutically acceptable salt form, e.g. suitable acid addition salts and quaternary ammonium salts. Such salts exhibit the same order of activity as the free bases. The present invention accordingly also provides a pharmaceutical composition comprising a compound of the invention, in free base form or an acid addition salt thereof or a quaternary ammonium salt thereof, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner so as to be for example a solution or a tablet.

The preferred compound is the title compound of Example 15 or 2.

A preferred group of compounds is these wherein A is a group of formula II wherein R_1 and R_2 independently are hydrogen, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy, R_2 is in position 4 or 5, R_3 is hydrogen or (C_{1-4})alkyl and the free bond is in position 3, 4 or 5. Another preferred group of compounds are those wherein A is a group of formula III wherein R_4 is hydrogen, halogen or (C_{1-4})alkoxy, R_5 is hydrogen or halogen or (C_{1-4})alkoxy, R_6 is amino, nitro, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, di(C_{1-4})alkylamino, halogen or 1-pyrrolyl and R_7 is hydrogen or halogen.

In a group of compounds A is a group of formula II wherein R_1 and R_2 independently are hydrogen, Y is $-NH-$ and the free bond is in position 3, or a group of formula III wherein R_4 is (C_{1-4})alkoxy, R_5 is hydrogen, R_6 is amino or alkylamino, R_7 is halogen, and D is a group of formula IV, V, VI, VII wherein t is 1, X, XI or XII wherein n,m,o and p is 0 or 1, and wherein R_8 is hydrogen or (C_{1-4})alkyl.

On one group of compounds D is a group of formula IV to XI. In another group of compounds D is a group of formula XII.

Conveniently when A is a group of formula III and B is NH then at least one to R_4 to R_7 is alkylamino.

Conveniently D is a group of formula IV or XII.

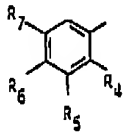
In a 1st group of compounds Y is $-CH_2-$.
In a 2nd group of compounds Y is $-NR_3-$.
In a 3rd group of compounds Y is $-O-$.
In a 4th group of compounds Y is $-S-$.
In a 5th group R_1 or R_2 is hydrogen.
In a 6th group R_1 or R_2 is halogen.
In a 7th group R_1 or R_2 is alkyl.
In a 8th group R_1 or R_2 is alkoxy.
In a 9th group R_1 or R_2 is hydroxy.
In a 10th group R_1 or R_2 is amino.
In a 11th group R_1 or R_2 is alkylamino.
In a 12th group R_1 or R_2 is alkylamino.
In a 13th group R_1 or R_2 is mercapto.
In a 14th group R_1 or R_2 is alkylthio.
In a 15th group R_3 is hydrogen.
In a 16th group R_3 is alkyl.
In a 17th group R_3 is alkenyl.
In a 18th group R_3 is aryl.
In a 19th group R_3 is arylalkyl.
In a 20th group one of R_4 to R_7 is hydrogen.
In a 21st group one of R_4 to R_7 is amino.
In a 22nd group one of R_4 to R_7 is nitro.
In a 23rd group one of R_4 to R_7 is alkylamino.
In a 24th group one of R_4 to R_7 is alkylamino.
In a 25th group one of R_4 to R_7 is halogen.
In a 26th group one of R_4 to R_7 is alkoxy.
In a 27th group one of R_4 to R_7 is alkyl.
In a 28th group one of R_4 to R_7 is alkanoylamino
In a 29th group one of R_4 to R_7 is pyrrolyl.
In a 30th group of compounds B is $-O-$.
In a 31st group of compounds B is $-NH-$.
In a 32nd group R_8 is hydrogen.
In a 33rd group R_8 is alkyl.
In a 34th group R_8 is alkenyl.
In a 35th group R_8 is aralkyl.
In a 36th group D is a group of formula IV.
In a 37th group D is a group of formula V.
In a 38th group D is a group of formula VI.
In a 39th group D is a group of formula VII.
In a 40th group D is a group of formula VIII.
In a 41st group D is a group of formula IX.
In a 42nd group D is a group of formula X.
In a 43rd group D is a group of formula XI.

CLAIMS

1. A process for the production of a compound of formula I

A–CO–B–D I

wherein A is a group of formula II or III

 II.  III

wherein the free valence is attached to either fused ring in formula II,

Y is $-CH_2-$, $-NR_3-$, $-O-$, or $-S-$,

R_1 and R_2 are independently hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, amino, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, mercapto or (C_{1-4})alkylthio,

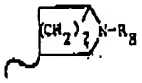
R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-5})alkenyl, aryl or arylalkyl,

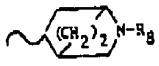
R_4 to R_7 are independently hydrogen, amino, nitro, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy, (C_{1-4})alkyl, (C_{1-4})alkanoylamino or pyrrolyl,

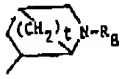
B is –O– or –NH–

D is a group of formula

 IV,

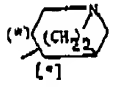
 V

 VI

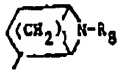
 VII

wherein t is 1 or 2,

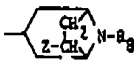
 VIII,

 IX

wherein the bond is in the position 3 (*) or 4(*),

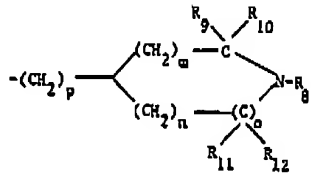
 X

wherein 1 is 2 or 3,



XI

wherein Z is (C_{1-4})Alkoxy,



XII

wherein

R_9 to R_{12} are independently hydrogen or (C_{1-4})alkyl,

m is 0, 1 or 2 and

n, o, p independently are 0 or 1.

wherein R_8 in each of formulae V to VII and X to XII is hydrogen, (C_{1-7})alkyl, (C_{3-5})alkenyl or aralkyl with the proviso that

1) when A is a group of formula III, and B is –NH–, then either D is a group of formula IV or R_6 is amino, (C_{1-4})alkylamino or di(alkyl(C_{1-4})amino and D is a group of formula XII other than 4-piperidinyl substituted by R_8 as defined above,

2) when A is a group of formula III, and B is –O– then D is other than a group of formula XII which is piperidinyl, pyrrolidinyl, pyrrolidinyl-2-methyl or azetidinyl, each substituted by R_8 as defined above,

3) when A is a group of formula II wherein Y is $-NR_3-$, –O– or –S–, R_3 is as defined above, and the free valence is in position 7 and B is –NH– then D is other than a group of formula V, X or XI,

4) when A is a group of formula II wherein Y is $-NR_3-$, R_3 is as defined above and wherein R_1 is in position 3 and is hydroxy or alkoxy, the free valence is in position 2 and B is –NH– then D is other than a group of formula XII which is pyrrolidinyl-2-methyl substituted by R_8 as defined above, and

5) when A is a group of formula II wherein Y is $-NR_3-$, R_3 is as defined above and wherein R_1 is in position 2 and is chlorine, bromine or substituted amino, the free valence is in position 3 and B is –O– then D is other than a group of formula XII which is a radical of formula $-(CH_2)_q-T$ wherein q is 0 or 1 and T is a 5 or 6 membered heterocyclic ring containing a nitrogen ring hetero atom or an acid addition salt or a quaternary ammonium salt thereof which includes the step of

a) condensing an appropriate compound of formula XIII

A–CO–OH XIII

wherein A is as defined above, a reactive derivative thereof, or a precursor of the acid or derivative, with an appropriate compound of formula XIV

H–B–D XIV

wherein B and D are as defined above, or a precursor of the compound or,

b) alkylating a compound of formula I having a secondary amino group to produce a compound of formula I with a tertiary amino group,

c) deprotecting any protected form of a compound of formula I to obtain a compound of formula I,

d) halogenating a compound of formula I wherein A is a group of formula II and R_1 is hydrogen to obtain the corresponding compound wherein R_1 is halogen, or

e) alkoxylating a compound of formula I wherein A is a group of formula II and R_1 is halogen to obtain the corresponding compound wherein R_1 is alkoxy, and

recovering the resultant compound of formula I as such or as acid addition salt or as a quaternary ammonium salt thereof.

2. A process for the production of a compound of formula I as defined in claim 1 or an acid addition salt or a quaternary ammonium salt thereof substantially as hereinbefore described.

3. A compound of formula I as defined in claim 1 or an acid addition salt or a quaternary ammonium salt thereof whenever produced by a process according to claim 1 or 2.

4. A compound of formula I as defined in claim 1 or an acid addition salt or a quaternary ammonium salt thereof.

5. A compound of claim 4 which is 1H-indo-3-yl-carboxylic acid (3R*, 4S*)-1-azabicyclo-[2.2.1]hept-3-yl ester or an acid addition salt or a quaternary ammonium salt thereof.

6. A compound of claim 4 which is (1H-indolyl-3-carboxylic acid 2S-(1-methyl-2-pyrrolidinyl-methyl) ester or an acid addition salt or a quaternary ammonium salt thereof.

7. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, the CO-group B is in the 3 position, B is −O− and D is a group of formula XI, wherein Z is OCH_3 and R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

8. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, the free valence is in the 3 position, B is −O− and D is a group of formula X, wherein 1 is 3 and R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

9. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the position, B is −O− and D is a group of formula V, R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

10. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula X, wherein 1 is 2, R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

11. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula X, wherein 1 is 3, R_8 is CH_3 and with the exo configuration or an acid addition salt or a quaternary ammonium salt thereof.

12. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula IV, and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

13. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula VII, wherein t is 1, R_8 is CH_3 and with the exo configuration or an acid addition salt or a quaternary ammonium salt thereof.

14. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula VI, R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

15. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 5 position, B is −O− and D is a group of formula XI, wherein Z is OCH_3, R_8 is CH_3 and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

16. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula IV, and with the exo configuration or an acid addition salt or a quaternary ammonium salt thereof.

17. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is NH, B is in the 3 position, B is −O− and D is a group of formula IV and with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

18. A compound of claim 9 in (+) optically active form or an acid addition salt or a quaternary ammonium salt thereof.

19. A compound of claim 9 in (−) optically active form or an acid addition salt or a quaternary ammonium salt thereof.

20. A compound of claim 4 wherein A is a compound of formula III wherein R_4 is OCH_3, R_5 is H, R_6 is $NHCH_3$ and R_7 is Cl, B is −NH−, D is a formula IV with the endo configuration or an acid addition salt or a quaternary ammonium salt thereof.

21. A compound of claim 4 wherein A is a compound of formula III wherein R_4 is OCH_3, R_5 is H, R_6 is $NHCH_3$ and R_7 is Cl, B is −NH−, D is a formula IV with the exo configuration or an acid addition salt or a quaternary ammonium salt thereof.

22. A compound of claim 6 in R form or an acid addition salt or a quaternary ammonium salt thereof.

23. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 1, n is 0, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

24. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 0, n is 1, o is 1, p is 1 or an acid addition salt or a quaternary ammonium salt thereof.

25. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 2, n is 0, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

26. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 1, n is 1, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

27. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is H, R_9, R_{10}, R_{11}, R_{12} are each CH_3, m is 1, n is 1, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

28. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −O−, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 2, n is 1, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

29. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is −NH−, the B is the 3 position, B is −NH−, D is a group of formula XII, wherein R_8 is H, R_9, R_{10}, R_{11}, R_{12} are each H, m is 1, n is 0, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

30. A compound of claim 4 wherein A is a group of formula II wherein R_1 and R_2 are each H, Y is —NH—, the B is the 3 position, B is —NH—, D is a group of formula XII, wherein R_8 is CH_3, R_9, R_{10}, R_{11}, R_{12} are each H, m is 1, n is 0, o is 1, p is 0 or an acid addition salt or a quaternary ammonium salt thereof.

31. A compound of claim 4 wherein A is a compound of formula III wherein R_4 is OCH_3, R_5 is H, R_6 is NH_2 and R_7 is Cl, B is NH, D is a group of formula XII wherein R_8 to R_{12} are each H, m is 1, n is 0, o is 1, p is o or an acid addition salt or a quartnery ammonium salt thereof.

32. A compound of claim 4 wherein A is a compound of formula III wherein R_4 is OCH_3, R_5 is H, R_6 is $NHCH_3$ and R_7 is Cl, B is NH, D is a group of formula XII wherein R_8 is CH_3 and R_9 to R_{12} are each H, m is 0, n is 1, p is 1, q is 1 or an acid addition salt or a quaternary ammonium salt thereof.

33. A compound according to claim 4 wherein A is a group of formula II wherein R_1 and R_2 independently are hydrogen, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy, R_2 is in position 4 or 5, R_3 is hydrogen or (C_{1-4})alkyl and the free bond is in position 3, 4 or 5 or an acid addition salt or a quaternary ammonium salt thereof.

34. A compound according to claim 4 wherein A is a group of formula III wherein R_4 is hydrogen, halogen or (C_{1-4})alkoxy, R_5 is hydrogen or halogen or (C_{1-4})alkoxy, R_6 is amino, nitro, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, halogen or 1-pyrrolyl and R_7 is hydrogen or halogen or an acid addition salt or a quaternary ammonium salt thereof.

35. A compound according to claim 4 wherein A is a group of formula II wherein R_1 and R_2 independently are hydrogen, Y is —NH— and the free bond is in position 3, or a group of formula III wherein R_4 is (C_{1-4})alkoxy, R_5 is hydrogen, R_6 is amino or alkylamino, R_7 is halogen, and D is a group of formula IV, V, VI, VII wherein t is 1, X, XI or XII wherein n, o and p is 0 or 1, and wherein R_8 is hydrogen or (C_{1-4})alkyl or an acid addition salt or a quaternary ammonium salt thereof.

36. A compound according to claim 4 wherein D is a group of formula IV to XI, A is a group of formula II wherein R_1 and R_2 independently are hydrogen, Y is —NH— and the free bond is in position 3, or a group of formula III wherein R_4 is (C_{1-4})alkoxy, R_5 is hydrogen, R_6 is amino or alkylamino, R_7 is halogen, and D is a group of formula IV, V, VI, VII wherein t is 1, X, XI or XII wherein n, o and p is 0 or 1, and wherein R_8 is hydrogen or (C_{1-4})alkyl or an acid addition salt or a quaternary ammonium salt thereof.

37. A compound according to claim 4 wherein D is a group of formula XII, A is a group of formula II wherein R_1 and R_2 independently are hydrogen, Y is —NH— and the free bond is in position 3, or a group of formula III wherein R_4 is (C_{1-4})alkoxy, R_5 is hydrogen, R_6 is amino or alkylamino, R_7 is halogen, and D is a group of formula IV, V, VI, VII wherein t is 1, X, XI or XII wherein n, o and p is 0 or 1, and wherein R_8 is hydrogen or (C_{1-4}) alkyl or an acid addition salt or a quaternary ammonium salt thereof.

38. A compound according to claim 4 wherein R_8 is alkyl or an acid addition salt or a quaternary ammonium salt thereof.

39. A compound according to claim 4 wherein A is a compound of formula II wherein the carbonyl group is in the 3 position.

40. A compound according to any one of claims 3 to 39 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof for use as a pharmaceutical.

41. A compound according to any one of claims 3 to 39 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof for use as a analgesic or anti-arrhythmic agent.

42. A compound according to any one of claims 3 to 39 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof for use as an anti-migraine agent.

43. A compound according to any one of claims 3 to 39 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof for use as a serotonin M antagonist.

44. A pharmaceutical composition comprising a compound according to any one of claims 3 to 39 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt in association with a pharmaceutical carrier or diluent.

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